REMARKS

Claims 98, 100, 106, 107, 109, 114, 115, 117, 120, 124, 125, 127, 128 and 142-146 are pending in the application. All claims have been rejected.

Claims 98, 100, 106, 107, 109, 114, 115, 117, 120, 124, 125, 127, 128 and 142-146 have been rejected under 35 USC 103(a) as being obvious over Garger et al. in view of Boller et al. and Frijters et al. Claims 98, 100, 106, 107, 109, 114, 115, 117, 120, 124, 125, 127, 128 and 142-146 have been provisionally rejected under 35 USC 101 for non-statutory double patenting as claiming the same invention as claims of co-pending US Application 11/790991. Claims 98-153 have now been canceled. New claims 154-167 have been added.

Claim Amendments

New claims 154-167 read on human glucocerebrosidase proteins, plant cells or pharmaceutical compositions comprising the same, comprising a human glucocerebrosidase protein having an amino acid sequence as set forth in SEQ ID NO: 8, wherein the protein is glycosylated with at least one exposed mannose, one alpha (1-3) fucose and at least one xylose, and further comprises a vacuolar targeting signal peptide as set forth in SEQ ID NO: 2 linked at the C-terminus. Amendments made to claims 98, 115, 142 and 146 in the previous communication (of July 27, 2009), including the limitation of specific vacuolar and endoplasmic reticulum signals SEQ ID NOs. 1 and 2, respectively, are now vacated, as these limitations were included in order to expedite prosecution, and in view of the allowance of the claimed subject matter indicated by the Examiner in the previous Office Action (of April 8, 2009).

The glucocerebrosidase protein of new claim 154 is supported throughout the instant specification, for example, Example 5 and Figures 6 and 7. Dependent claims 155- 182 correspond to previous claims as follows:

New Claim	Previous Claim (in communication of May 7, 2008)
155	See Ex 1 and page 20, lines 24-27
156	108, 105
157	See page 26, lines 19-27
158	134, and See Example 3 and Fig. 5A
159	See Examples 3 and 5
160	114, 144
161-164	115-126
165	Example 5 and Figs. 6 and 7
166, 167	See page 12, line 28 to page 13, line 4

No new subject matter has been introduced.

35 U.S.C. § 103 Rejections: Garger (US Patent Application No:09/993059), in view of Boller (US 6054637) and Frijters (NL-1012782).

The Examiner has rejected claims 98, 100, 106, 107, 109, 114, 115, 117, 120, 124, 125, 127, 128 and 142-146 under 35 USC 103(a) as allegedly being unpatentable over Garger et al. ("Garger"), in view of Boller et al. ("Boller") and Frijters et al. ("Frijters"). The Examiner's rejections are respectfully traversed. Claims 98-153 have now been canceled. New claims 154-167 have been added.

Claim 154, and all the remaining claims in this case (which depend directly or indirectly from claim 154), requires a human glucocerebrosidase ("GCD") protein that comprises the amino acid sequence set forth in SEQ ID NO: 8, is glycosylated and comprises at least one exposed mannose, at least one fucose having an alpha (1-3) glycosidic bond and at least one xylose and is linked at its C-terminus to a vacuolar targeting signal peptide as set forth in SEQ. ID. NO.: 2. The specification teaches that directing the GCD protein into the plant vacuole unexpectedly results in a GCD protein with these modifications and that is biologically active (paragraph 29):

> "Surprisingly, the transformed plant root cells of the present invention produced an unexpected high mannose GCD. Advantageously, this high mannose product was found to be biologically active and therefore no further steps were needed for its activation. Without wishing to be limited by a single hypothesis, it would appear that the use of an ER signal with the recombinant protein being produced in plant cell culture was able to overcome transportation to the Golgi, and hence to retain the desired high mannose glycosylation."

There is no suggestion or any indication from the combination of references to direct GCD to the vacuole of plant, let alone that causing GCD to be directed to the vacuole would result in a uniquely glycosylated GCD that is biologically active without further processing steps.

The Examiner alleges that Garger teaches recombinant production of human glucocerebrosidase identical to SEQ ID NO: 8 in transgenic tobacco plants, that Boller teach the advantages of the use of signal peptides for vacuolar sorting of proteins, including SEQ ID NO: 2, and that Frijters teaches an ER signal peptide sequence identical to SEQ ID NO: 1, and that one of ordinary skill in the art would have found it obvious to make a fusion protein comprising the human glucocerebrosidase of

Garger, with the vacuolar signal protein of Boller and the endoplasmic reticulum signal sequence as disclosed by Frijters. Applicant disagrees.

1. Garger teaches away -- targeting plant-expressed lysosomal enzymes for secretion into the interstitial fluid of whole plants.

Garger is directed to providing "a recombinant system…that can produce human or animal lysosomal enzymes in an active form at lower cost, and that will be appropriately targeted for ease of recovery" (Garger, [0034]). Garger attempts to achieve this by directing the protein to be secreted into the interstitial fluid (see [0104]) -- rather than directing the protein into the vacuole. To this end, Garger specifically teaches away from use of "redundant sorting signals" in the native lysosomal polypeptide (Garger, [0106]) and directs the ordinarily skilled artisan to delete these C-terminal sequences to prevent vacuolar sorting (Garger, [0277]). In fact, Tables 8, 9 and 11 of Garger show the increased recovery from the interstitial fluid of C-terminal truncated α-galactosidase from tobacco leaves. Garger summarizes the results in [0284]. Specifically, Garger reports that enzymatically active, plant-expressed human glucocerebrosidase, including the native human N-terminal signal peptide, was accurately expressed, processed and secreted to the interstitial fluid of tobacco plants (Garger [0164] – [0166]).

Garger also report that the secreted glucocerebrosidase was apparently glycosylated (Garger [0125] and [0164]. Applicants note that the human glucocerebrosidase as taught by Garger does not have the exposed mannose glycan structure of the glucocerebrosidase protein recited in new claims 154-167.

The Examiner acknowledges that Garger does not teach the use of a vacuolar targeting signal in its method of expressing glucocerebrosidase (see page 6 of the February 18, 2010 Office Action). In fact, Garger teaches directly away from using a vacuolar targeting signal. Garger teaches that presumptive vacuolar-targeting sequences should be deleted from transgenic lysosomal enzymes expressed into the instersitial fluid of plants (paragraph 277, emphasis added):

> "For several plant proteins vacuolar sorting information is located in a carboxy-terminal propeptide (CTPP; 37,38). During the original cloning and characterization of human Gal-A, Quinn et al., postulated a cathepsin-like potential

> CTPP cleavage for this enzyme at or near two arginine residues, 26 and 28 AA from the termination codon (39,40). The precise AA sequence at the carboxy terminus has, to our knowledge, never been reported. Because secretion in the plant leaf is through a default pathway **we reasoned that deletion of specific sorting information from a postulated CTPP might yield more active enzyme in the IF**. Analysis of a second set of constructs containing either 12 or 25 AA truncations, with and without the ER retention signal provided dramatic evidence for the significance of this region (See Table 9). In one construct, rGal 12-SEKDEL, virtually all of the CRIM is now assembled and stored as fully active enzyme and is secreted to the IF in significant quantities."

For these reasons, Garger expressly teaches away from use of a vacuolar targeting sequence as claimed here.

2. The Ordinarily Skilled Artisan would not combine Boller with Garger.

First, Boller does not teach the expression of any mammalian or human polypeptides in plant cells, and certainly not GCD.

Second, in view of the express teaching in Garger to not use a vacuolar targeting sequence, the ordinarily skilled artisan would not combine Garger with Boller, which is cited for teaching a vacuolar-targeting peptide.

Moreover, Boller notes that "Proteins that do not contain an additional signal are apparently secreted automatically into the extracellular space..." (Boller, column 2, line 32-35) and teaches the deletion of the vacuolar targeting signal sequence as a means for targeting expression products to the intercellular or extracellular space as called for by Garger (see, for example, Boller, column 18, line 53, to column 19, line 4):

> "In a second variant, the C-terminal extension of a basic chitinase gene...is removed...or at least inactivated. ***As a result, the gene product is secreted into the intercellular space...***"
> "A further aspect of the present invention...relates to recombinant DNA molecules...in which the 3' terminal targeting sequence...has been deleted or otherwise removed. On transformation into a plant host, ***these constructs produce an expression product that does not contain a functional C-terminal signal sequence and is therefore secreted into the extracellular space***."

Finally, Boller was published some nine years before Garger and yet Garger expressly taught away from use of vacuolar targeting sequences, even though they had been known for several years and are even specifically noted by Garger itself. This further demonstrates the lack of recognition in the art of the invention claimed here. For at least these reasons, Garger cannot be combined with Boller and/or Frijters to produce the protein now claimed.

For these reasons, one of ordinary skill in the art with Garger in hand, would not be motivated to combine the secreted lysosomal protein as taught in Garger with the vacuolar targeting signal for use with naturally occurring plant proteins as taught by Boller for production of the claimed human recombinant glucocerebrosidase protein (and plant cells and pharmaceutical compositions comprising said protein).

The deficiencies of Garger and Boller are not remedied by Frijters. Frijters is silent regarding lysosomal enzymes, and does not teach or motivate vacuolar targeting of plant expressed enzymes. Frijters merely reports the sequence of an ER targeting signal as set forth in SEQ ID NO: 1 of the instant specification.

A determination of obviousness cannot be based on the hindsight combination of components selectively culled from the prior art to fit the parameters of the patented invention [see Crown Operations Int'l, LTD v. Solutia Inc., 289 F.3d 1367 (Fed. Cir. 2002)], and 35 U.S.C. § 103 specifically requires consideration of the claimed invention "as a whole" in making the assessment of differences [see Envtl. Designs, Ltd. v. Union Oil Co., 713 F.2d 693 (Fed. Cir. 1983)], the "as a whole" instruction in 35 U.S.C. § 103 prevents evaluation of the invention part by part, Applicant submits that Garger cannot be reasonably combined with Boller, with or without Frijters to produce the claimed human glucocerebrosidase protein. Withdrawal of the rejections based on obviousness is respectfully requested.

While strongly traversing the Examiner's rejection of the claims on the basis of the combination of Garger, Boller and Frijters, as detailed herein, and solely in order to expedite prosecution in this case, Applicant has amended claim 155 to include the limitation of the human glucocerebrosidase protein being linked at its C terminus to a vacuolar signal peptide as set forth in SEQ ID NO: 2. Applicant believes that such an amendment now further distinguishes the claimed human glucocerebrosidase protein, compositions and cells expressing the same, from any polypeptides taught, suggested or inferred by any of Garger, Boller or Frijters, alone or in combination.

Double Patenting

The Examiner has rejected claims 98, 100, 106, 107, 109, 114, 115, 117, 120, 124, 125, 127, 128 and 142-146 on the grounds of provisional double patenting as claiming the same invention as claims 39 and 45 of co-pending US Patent Application No. 11/790991.

The Examiner has also rejected claims 114 and 142-144 on the ground of non-statutory obviousness type double patenting for being unpatentable over claims 39 and 45 of co-pending US Patent Application No. 11/790991. Claims 98-153 have now been canceled, rendering moot the Examiner's rejections thereof.

Issues of provisional and obviousness-type double-patenting and the submission of a terminal disclaimer will be further considered with respect to US Patent Application No. 11/790991 upon indication by the Examiner of allowable claims in the present case.

Corresponding Patent Applications

Applicant wishes to make of record the communication dated July 23, 2010 from the EPO with regard to corresponding European Patent Application No. 04713966.2. All the material references cited in the 04713966.2 application have been made of record in the subject application. Applicants believe that they have fully complied with the Federal Circuit court's concerns raised in *McKesson Information Solutions v. Bridge Medical, Inc.* 82 U.S.P.Q.2D (BNA) 1865 (2007).

In view of the foregoing amendments and remarks, new claims 154-167 are deemed to be allowable. Their favorable reconsideration and allowance is respectfully requested.

Respectfully submitted,

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Date: August 17, 2010

Enclosures:

- Petition for Extension (Three Months)
- EP OA 04713966.2 dated July 23, 2010